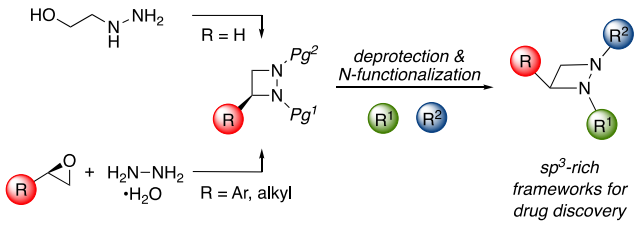
Graphical Abstract:



Title:
Synthesis of sp^3-rich Chemical Libraries based upon 1,2-Diazetidines

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sp^3-rich scaffold; chemical library; hydrazine; 1,2-diazetidine; epoxide opening

Dedication:
Dedicated to the memory of Jonathan Williams: a wonderful colleague, mentor and friend

Abstract:
A strategy for the creation of sp^3-rich, non-planar scaffolds for drug discovery is described. Stereocontrolled ring opening of homochiral 1,2-epoxides by hydrazine monohydrate followed by selective protection of both nitrogen atoms and Mitsunobu ring closure gives differentially protected, enantiomerically pure 1,2-diazetidines (up to 98% ee) bearing a variety of C-3 substituents. Iterative C–N functionalization at the two nitrogen atoms using a range of chemistries and coupling partners produces a 1,2-diazetidine based chemical library. Crystallographic data confirm that these frameworks display significant sp^3-character with the nitrogen substituents adopting an *anti*-configuration.

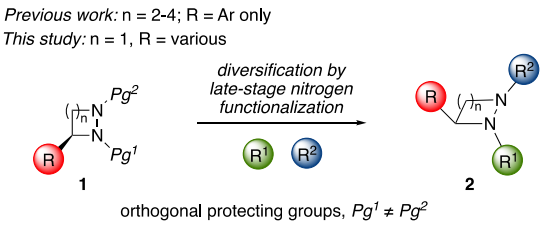
1. Introduction

Success in drug development has been shown to correlate with molecular complexity, as measured by parameters such as the fraction of saturated carbon atoms (Fsp^3) and number of stereogenic centers.[1,2] Consequently, chemical libraries of small molecules capable of exploring new areas of three-dimensional space have much potential in drug discovery. Contemporary drug-like libraries such as the ChEMBL dataset often display inadequate shape diversity and three-dimensionality,[2] and hence there is a need to create new stereochemically-rich compound libraries for application in drug-discovery programs.[3]

Recently, we introduced a simple way to create chemical libraries with considerable shape diversity without the need to produce multiple stereogenic centers with independent control.[4] Novel libraries were constructed from enantiopure cyclic hydrazine **1** by sequential functionalization of each nitrogen atom using a range of C–N bond forming reactions (Scheme 1). Crucially, the fluxional behavior of the pyramidal nitrogens within the resultant sp^3-rich heterocyclic framework **2** allowed it to adopt a well-defined conformation in which each

added fragment (R, R^1 and R^2) project away from its neighbors to minimize repulsive interactions.[4] Using this approach, chemical libraries displaying three-dimensionality and shape diversity could be readily generated.

Scheme 1. New sp^3-rich cyclic hydrazine frameworks for drug discovery.

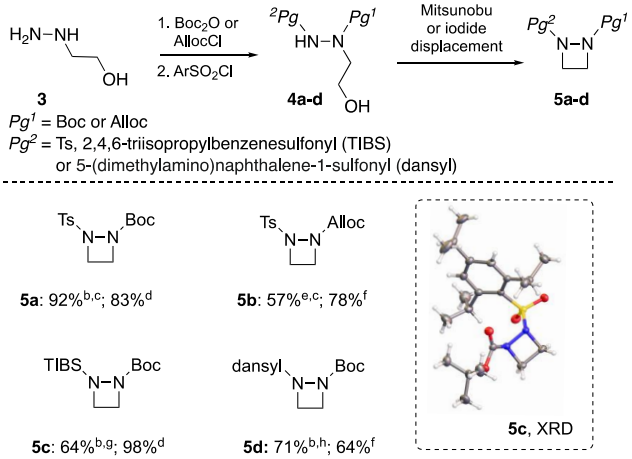


In this earlier work, we focused on chemical libraries based upon larger hydrazine ring sizes (n = 2-4). We also reported the synthesis of several derivatives of **1** (n = 1), but only successfully converted it to **2** in the special case of R^2 = H. In this article, we sought to overcome this limitation by expanding the work to include the construction of libraries based on 1,2-diazetidines (i.e. **2**, n = 1). Importantly, we felt that the use of four-membered ring scaffolds might offer several potential advantages. Firstly, due to their lower molecular weight, a greater proportion of the members of the resultant chemical libraries would be lead-like (MW <350), making them more useful in drug discovery.[5] Secondly, derivatives based on four-membered rings possess greater nitrogen pyramidalization due to ring strain, offering distinct shapes in comparison to their larger homologs.[6] Thus, a chemical library including 1,2-diazetidines should benefit from increased shape diversity overall. Finally, for this specific ring size, we anticipated new methods of synthesis would be available allowing the introduction of a much broader range of fragments (R = H, alkyl and aryl) into starting material **1** with defined stereocontrol.

2. Results and Discussion

Initial work focused on the synthesis of 1,2-diazetidines **5a-d** from commercially available 2-hydroxyethylhydrazine (**3**) bearing different protecting groups on the two nitrogen atoms (Scheme 2).[7] The synthesis began with conversion of **3** in two steps to **4a-d** by selective introduction of a carbamate group (Boc or Alloc) at the more nucleophilic nitrogen, followed by sulfonylation (Ts, TIBS or dansyl) at the remaining nitrogen of the hydrazine.[8] Final ring closure to the 1,2-diazetidine was achieved in good yield either by Mitsunobu reaction (**4a** and **4c**) or via the corresponding iodide (**4b** and **4d**). In the Mitsunobu process, either diethyl azodicarboxylate (DEAD) or less hazardous diisopropyl azodicarboxylate (DIAD) can be used. The two-step cyclization via the iodide was preferred in cases when the Mitsunobu by-products proved difficult to remove by chromatography. For **4c**, we were able to unambiguously confirm its structure by single crystal x-ray diffraction (XRD).[9]

Scheme 2. Synthesis of differentially protected 1,2-diazetidines.[a]



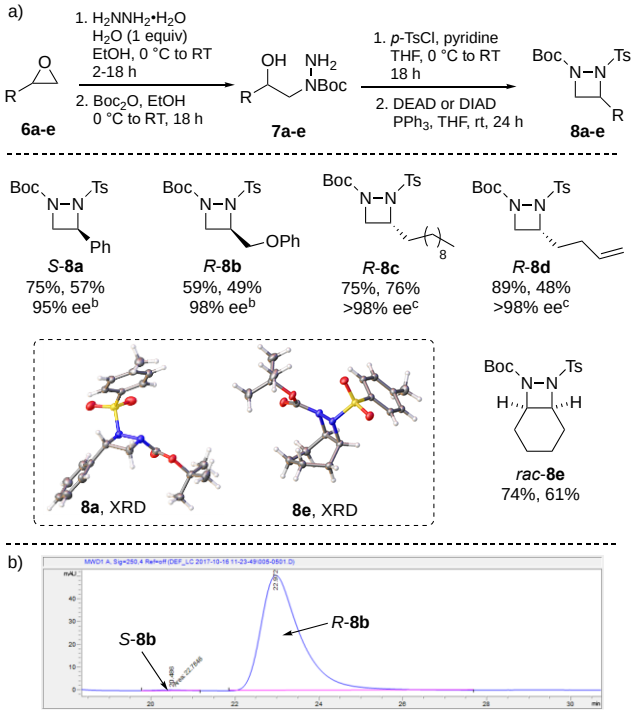
a. Isolated yields correspond to the synthesis of **4** and **5**, respectively
b. Boc_2O, EtOH, RT, o/n
c. TsCl, pyr, THF, RT, o/n
d. DEAD or DIAD, PPh_3, THF, RT, o/n
e. AllocCl, Et_3N, CH_2Cl_2, RT, o/n
f. I_2, PPh_3, imidazole, THF, RT, 1 h; then Cs_2CO_3, MeCN, RT, o/n
g. TIBSCl, pyr, THF, RT, o/n
h. DansylCl, pyr, THF, RT, o/n

Next, we examined the synthesis of 1,2-diazetidines bearing a carbon substituent at C-3. Several synthetic routes to enantiomerically enriched 3-substituted 1,2-diazetidines have been described.[4,10–14] Ma has reported the diastereoselective synthesis of 3,4-disubstituted 1,2-diazetidines via Pd-catalyzed cyclization of chiral 2,3-allenyl hydrazines with aryl halides in good yields.[10] Iacobini *et al.* made 3-methyl 1,2-diazetidines by Rh-catalyzed asymmetric hydrogenation of 3-methylene-1,2-diazetidines.[11a] Rajkumar *et al.* have developed a route to 3-vinyl derivatives via Pd-catalyzed asymmetric allylic amination of racemic vinyl epoxide,[14] and most recently, we reported an enantiocontrolled route to 3-aryl 1,2-diazetidines using asymmetric transfer hydrogenation (ATH) as the key step.[4] Despite these advances, no single method is suitable for the introduction of both aryl and alkyl substituents, and a new more general route was sought for our needs.

To this end, we explored the controlled ring-opening of enantiomeric enriched epoxides with hydrazine hydrate at the unsubstituted carbon atom.[15] Enantiomeric enriched epoxides **6a-d** were either commercially available or easily accessible by hydrolytic kinetic resolution (HKR).[16] After ring opening, the secondary nitrogen was selectively protected with a Boc group to give **7a-d**, which was further converted into **8a-d** by tosylation of the primary nitrogen and azodicarboxylate mediated Mitsunobu cyclisation (Scheme 3a).[7] This epoxide ring-opening strategy towards C-3 substituted 1,2-diazetidines was suitable for aryl as well as alkyl substituents. Starting from enantiomeric enriched starting materials, C-3 substituted diazetidines **8a-d** were obtained in >95% ee as illustrated by the HPLC trace of enantiomeric enriched **8b** (Scheme 3b).[7] The absolute stereochemistry of **8a** was confirmed by comparison

with literature data,[4] and the other examples assigned by analogy. In addition, the method can be extended to annulated *rac*-**8e** using the same sequence starting from *meso*-cyclohexane epoxide (**6e**).[17] XRD structures of **8a** and **8e** clearly show an *anti*-configuration of the nitrogen protecting groups with the latter structure displaying a boat conformation of the annulated cyclohexane ring (Scheme 3, box insert).

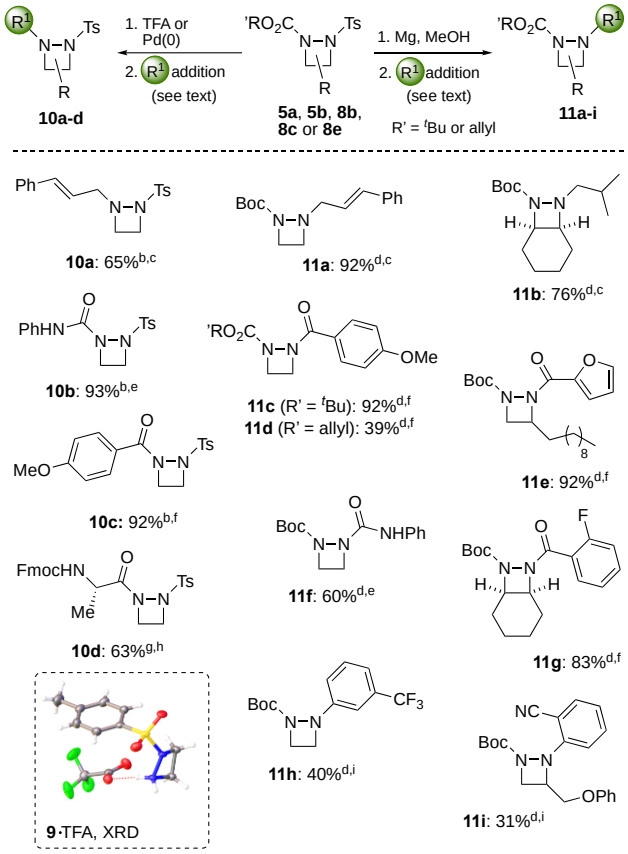
Scheme 3. Stereocontrolled synthesis of 3-substituted 1,2-diazetidines.[a]



a. Isolated yields correspond to the synthesis of **7** and **8**, respectively
b. Enantiomeric excess determined by chiral HPLC[7]
c. Enantiomeric excess determined after deprotection of the Boc group[7]

Next, we sought to build libraries from these differentially protected 1,2-diazetidines as illustrated in Scheme 1. This necessitates being able to introduce a variety of substituents at both nitrogen atoms in a controlled, iterative manner. To this end, we explored chemistries suitable for the first functionalization step, by removal of either the sulfonyl or carbamate N-protecting group. Starting from **5a**, the Boc group could selectively be removed with trifluoroacetic acid to give the mono-protected TFA salt **9** (Scheme 4, box insert); neutralizing the acid with a sodium bicarbonate wash provided the free amine. Starting from Alloc protected diazetidine **5b**, treatment with $Pd(PPh_3)_4$ and phenylsilane provided the same intermediate. This compound could be successfully functionalized by reductive amination (**10a**), reaction with an isocyanate (**10b**), acylation (**10c**) or HATU-mediated coupling to Fmoc-Ala-OH (**10d**) in good to excellent yields over the two steps.[7] Alternatively, the tosyl group from five representative 1,2-diazetidines (**5a, 5b**, **8b**, **8c** and **8e**) was selectively removed with magnesium in methanol and derivatized using an even wider range of chemistries. Reductive amination (**11a**, **11b**), acylation (**11c-e**, **11g**), trapping with phenyl isocyanate (**11f**), and Buchwald-Hartwig coupling (**11h**, **11i**) were all successfully applied to these substrates. Whilst Alloc-protected **5b** could be used, the more modest yields seen in the formation of **10d** and **11d** led us to conclude that Boc protection was a superior choice.

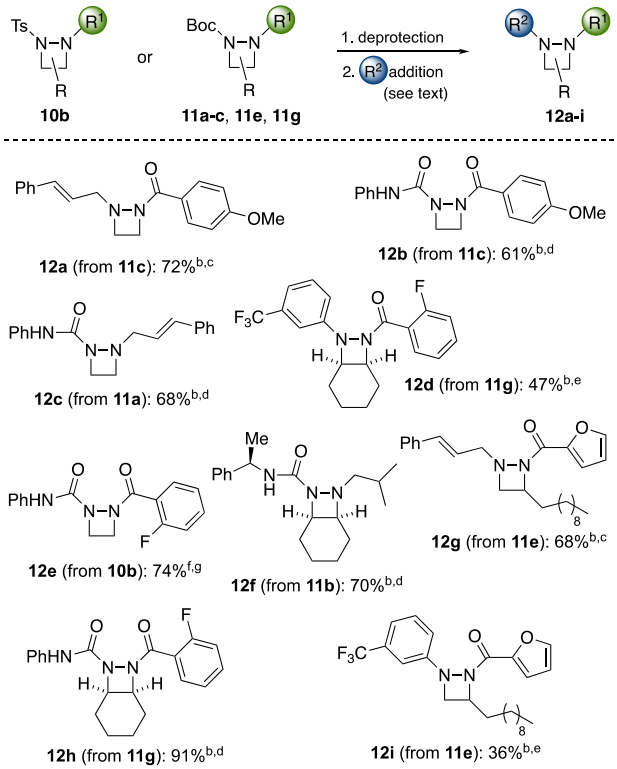
Scheme 4. Selective deprotection/monofunctionalization of 1,2-diazetidines.[a]



a. Isolated yield over 2 steps
b. TFA, CH_2Cl_2, RT, 2h; then $NaHCO_3$
c. RCHO, $NaBH(OAc)_3$, THF, RT, o/n
d. Mg, MeOH, RT, 2h
e. PhNCO, CH_2Cl_2, RT, o/n
f. RCOCl, $^iPr_2EtN$, CH_2Cl_2, RT, o/n
g. $Pd(PPh_3)_4$, $PhSiH_3$, CH_2Cl_2, RT, 2h
h. Fmoc-Ala-OH, HATU, $^iPr_2EtN$, CH_2Cl_2, RT, o/n
i. $Pd(OAc)_2$, ArBr, Xantphos, NaO^tBu, PhMe, 90 °C, o/n

Next, we explored the more demanding second functionalization step (Scheme 5).[7] In this case, both the steric and electronic demands of the substrates vary as a function of the nature of the substituent introduced during the first functionalization. Despite this added complexity, we were able to use all the chemistries described above to produce **12a-i** in yields ranging from 36-91% over the two-step process (average yield 65%). Indeed, the approach works across a range of diazetidine frameworks including unsubstituted, 3-substituted and annulated systems.

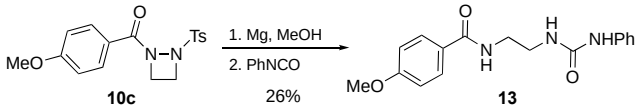
Scheme 5. Second functionalization of 1,2-diazetidines.[a]



a. Isolated yield over 2 steps
b. TFA, CH_2Cl_2, RT, 2h; then $NaHCO_3$
c. RCHO, $NaBH(OAc)_3$, THF, RT, o/n
d. RNCO, CH_2Cl_2, RT, o/n
e. $Pd(OAc)_2$, ArBr, Xantphos, NaO^tBu, PhMe, 90 °C, o/n
f. Mg, MeOH, RT, 2h
g. RCOCl, $^iPr_2EtN$, RT, o/n

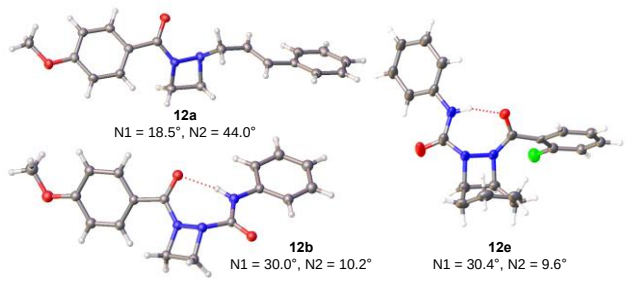
It is possible to remove and functionalize the Boc and Ts nitrogens in any order. However, generally we have observed better yields and fewer side products across a range of substrates and chemistries when the Ts group is removed first. Reversing this order can lead to unwanted side reactions, as illustrated in Scheme 6. Attempted Ts deprotection and derivatization of **10c** led to diamine **13** in low yield, instead of the expected 1,2-diazetidine **12b**. This product presumably arises from reductive cleavage of the N–N bond during treatment with magnesium in methanol to cleave the Ts group, with **13** produced after trapping of the resultant primary amine with PhNCO. The structure of this compound was established by NMR spectroscopy and confirmed by single-crystal XRD.[7] Interestingly, more forcing conditions such as Raney Ni and hydrogen are normally required to cleave the N–N bond of 1,2-diazetidines,[14] suggesting that this behavior is substrate dependent. The electron rich aryl group and amide seem to make substrate **10c** more prone for this undesired pathway, no reductive cleavage was observed for diazetidine **10b** under the same reaction conditions.

Scheme 6. Unexpected ring cleavage reaction.



For three of the final products (**12a**, **12b** and **12e**) we were able to determine their solid-state structures by X-ray crystallography (Figure 1). In each case, the N-substituents displayed the expected *anti*-disposition and significant nitrogen pyramidalization contributing to their three-dimensionality.[18] In the case of **12b** and **12e**, an intramolecular hydrogen bond was observed between the appended nitrogen fragments.

Figure 1. Representative XRD structures of difunctionalized 1,2-diazetidines with measured values for the pyramidalization of the two ring nitrogens (N1 and N2).[18]



3. Conclusions

New strategies for the synthesis of differentially protected 1,2-diazetidines have been developed based on Mitsunobu ring closure of 2-hydroxyethylhydrazine derivatives. This chemistry was successfully combined with the stereocontrolled ring opening of homochiral 1,2-epoxides by hydrazine monohydrate to realize the first practical synthesis of differentially-protected, enantiomerically pure 1,2-diazetidines bearing either an alkyl or aryl substituents at C-3. The methodology further provides access to annulated diazetidines as illustrated by the synthesis of *rac*-**8e** from cyclohexane epoxide. A total of 9 differentially protected 1,2-diazetidines were prepared through variation in the C-3 substituents and nitrogen protecting groups. The chemistry is operationally simple and can be performed on a preparative scale. Chemical library construction from these 1,2-diazetidines is possible by iterative C–N bond formation at the two nitrogen atoms. Best results are achieved using substrates bearing Boc and Ts groups using a sequence that involves initial removal of the Ts group. Chemical diversification is possible through variation in the structure of the heterocycle, use of different functionalization chemistries and coupling partners, and controlled engagement of each nitrogen of the hydrazine in turn. X-ray crystallography performed on three members of the final library reveal useful insights into how the molecules sample chemical space. In all cases, the nitrogen substituents adopt the expected *anti*-configurations and display significant sp^3-character at nitrogen. Future work will examine the

feasibility of making larger chemical libraries based on these non-planar scaffolds and the exploitation of them in drug discovery programs.

4. Experimental

All experimental procedures and characterization data for the new compounds, copies of HPLC traces, ^{1}H and ^{13}C NMR spectra and XRD structures are provided in the Supplementary data.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at "*add doi here"*.

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